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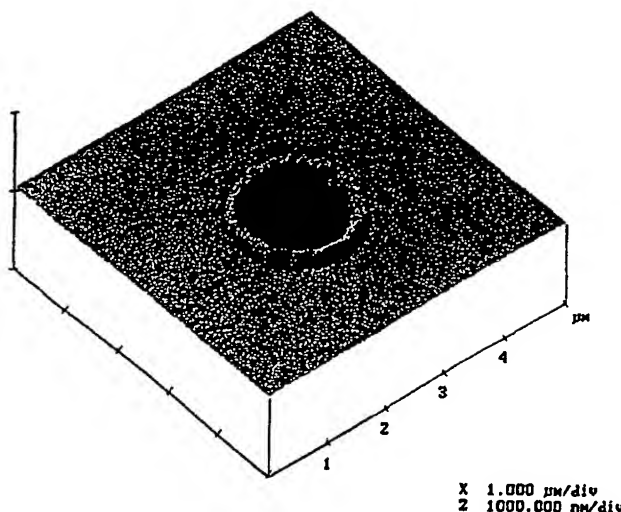
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(54) Title: METHOD OF FABRICATING POROUS MEMBRANE WITH UNIQUE PORE STRUCTURE FOR AEROSOLIZED DELIVERY OF DRUGS



(57) Abstract

A method for producing a nozzle useful in generating a fine aerosol for delivery of therapeutic or diagnostic agents is provided. The method comprises focusing a laser source onto a thin, preferably flexible material so as to form pores substantially through the material. The pores are formed to have an unflexed exit aperture diameter in the range of about 0.5 to about 25 microns, depending on the size of the aerosol particles desired for a particular application. The nozzle may have a variety of shapes and be distributed in a variety of patterns. An elevated area can be formed around the exit aperture of the nozzle in order to prevent intrusion of liquid into the nozzle.

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METHOD OF FABRICATING POROUS MEMBRANE WITH UNIQUE PORE STRUCTURE FOR AEROSOLIZED DELIVERY OF DRUGS

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BACKGROUND OF THE INVENTION

Aerosolization is a desirable means for the delivery of therapeutic or diagnostic agents. Aerosol delivery avoids the problems associated with other delivery methods such as oral administration or injection. Injections are painful, present a risk of infection to the health-care provider from an inadvertent needle-stick, and create hazardous waste from the needle and syringe. Additionally, repeated injections can result in scarring. Oral administration must overcome several obstacles to the delivery of agents, including the acidic environment of the stomach, the ability of the agent to pass through the of the intestinal wall, and first-pass metabolism of the agent by the liver. Aerosol delivery, on the other hand, allows the direct delivery of agents to areas such as the nasal tract, the respiratory tract, or the eye, as well as systemic delivery into the circulation by administration to the respiratory tract and uptake into the circulation.

Prior methods of generating and delivering aerosols to the nasal and respiratory tract include metered-dose inhalers, dry powder inhalers and nebulizers. Prior methods of delivering agents to the eye include ointments and eyedrops. Administration of agents to the eye can lead to improper dosing due to blinking and drainage, and the squeamishness about inserting things into the eye can lead to problems with patient compliance.

Difficulties with prior methods of delivering aerosols include the inefficient use of materials being aerosolized, the lack of uniformity in the size of the particles generated, and the inability to direct the administered agent to a particular location within the respiratory tract. Additionally, metered-dose inhalers may use propellants which adversely affect the ozone layer.

A method of generating aerosols of defined particle size is therefore desirable in order to provide a more efficient and more controllable means of delivering therapeutic or diagnostic agents to a target tissue. A portable, reproducible means of providing such aerosols would also increase patient mobility and decrease health care expense by decreasing the need for expensive immobile equipment and monitoring costs associated with regulating the dosages received from inefficient devices.

Devices and methods for controlling aerosol particle size are known in the art. For example, US 4,926,852 described control of particle size by metering a dose of medication into a flow-through chamber that has orifices to limit the flow rate. US 4,677,975 described a nebulizer device having baffles to remove particles above a selected size from an aerosol. US 3,658,059 employed a baffle that changes the size of an aperture in the passage of the suspension being inhaled to select the quantity and size of suspended particles delivered. US 5,497,944 described a method and device for generating an aerosol by passing the formulation through a small nozzle aperture at high pressure. However, devices that process the aerosol particle size after generation (e.g., by filtering the aerosol after it is formed from the formulation) are typically inefficient, wasteful, and/or require a substantially greater amount of force to generate the aerosol.

Co-owned U.S. Patent 5,544,646 and U.S. Patent applications serial numbers 08/454,421, 08/630,391, 08/693,593 and 08/804,041 describe devices and methods useful in the generation of aerosols suitable for drug delivery. A drug formulation is forcibly applied to one side of the pore-containing membrane so as to produce an aerosol on the exit side of the membrane. Aerosols containing particles with a more uniform size distribution can be generated using such devices and methods, and can be delivered to particular locations within the respiratory tract.

Improved porous membranes for use in such devices would allow more efficient use of formulations, thereby requiring packaging of less formulation, and decreasing costs and increasing portability and patient compliance. These porous membranes can be of improved size, shape or arrangement. Thus there is a need for methods of producing nozzles for use in the aerosolization of diagnostic or therapeutic agents. There is a further need for aerosolization devices which are lightweight, portable and provide for precise aerosol particle size which can be targeted to a specific tissue.

SUMMARY OF THE INVENTION

We have now invented a method of forming nozzles of small, uniform size that permit the generation of uniform aerosols of diagnostic and therapeutic agents which can then be administered to particular target tissues such as the eye or specific areas of the respiratory tract. The method comprises directing a laser source onto a thin preferably flexible material so as to form pores substantially through the material. The pores may be formed either

individually or simultaneously. The laser source may be controlled using a mask and/or beam-splitting or focusing techniques. In one embodiment, the pores are formed completely through the membrane. In another embodiment, the pores are formed so that a thin layer remains covering the exit side of the pore; this layer can then be burst outwards upon
5 administration of a formulation at a pressure substantially below that which would rupture the remainder of the membrane. In another aspect of the invention, the pores are formed so as to have an entrance aperture that is larger than the exit aperture.

In one aspect of the invention, a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser is used as the laser source. In another aspect of the invention, an excimer
10 laser is used as the laser source. In still another aspect of the invention, the pores are formed so as to have an exit aperture of from about 0.5 to about 25 μm in diameter.

In an additional aspect of the invention, a method of producing a nozzle for aerosolizing a formulation is provided wherein from about 200 to about 1,000 holes are formed in a membrane by projecting an excimer laser or focusing a YAG laser onto the
15 membrane in a manner and for a time sufficient to ablate pores substantially through the membrane. In a particular embodiment, holes having an average relaxed exit aperture diameter of from about 0.5 to about 1.5 μm and spaced from about 30 to about 70 μm apart from each other can be formed in the membrane for the formation of particles for aerosol delivery to the respiratory tract.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic drawing of an excimer laser apparatus used to ablate pores in a material using the method of the invention.

Figure 2 is a scanning electron micrograph of the exit aperture of a pore formed by the
25 methodology of the present invention so as to have an elevated area surrounding the exit aperture to prevent intrusion of the formulation back into the pore.

Figure 3 is a graph of the aerosol quality vs. pore size for porous membranes generated by the method of the present invention.

30 DESCRIPTION OF THE PREFERRED EMBODIMENTS

Before the present methods of fabricating porous membranes for aerosolized delivery of drugs are described, it is to be understood that this invention is not limited to the particular

methodology, devices, containers and formulations described, as such methods, devices, containers and formulations may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the
5 appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a formulation" includes mixtures of different formulations, reference to "an asthma attack" includes one or more of such events, and reference to "the
10 method of treatment" and to "the method of diagnosis" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

Where a range of values is provided, it is understood that each intervening value between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or
15 intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller range is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or
20 both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are
25 now described. All publications mentioned herein are incorporated herein by reference to describe and disclose specific information for which the reference was cited.

The publications discussed above are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.
30

DEFINITIONS

The terms "package" and "disposable package" are used interchangeably herein and shall be interpreted to mean a container or two or more containers linked together by an interconnecting means wherein each container preferably includes one or more channels
5 which provide for fluid connection from the container to a nozzle comprised of a porous membrane, which nozzle is preferably not positioned directly over the container, and wherein each container includes at least one surface that is collapsible in a manner so as to allow the forced displacement of the contents of the container through a low resistance filter and out the nozzle (without rupturing the container) in a manner such that the contents are
10 aerosolized. There are at least two variations of the package, depending on whether the drug can be stably stored in a liquid form or must be stored dry and combined with liquid immediately prior to aerosolization.

The contents of each container preferably comprises a formulation, preferably a flowable formulation, more preferably a liquid, flowable formulation, which includes a
15 pharmaceutically active drug or a diagnostic agent. If the drug or diagnostic agent is not liquid and of a sufficiently low viscosity to allow the drug to be aerosolized, the drug or diagnostic agent is dissolved or dispersed in an excipient carrier, preferably without any additional material such as preservatives that might affect the patient. When the contents must be stored in a dry state, the package further includes another container that holds the
20 liquid and can be combined with the dry drug immediately prior to administration.

The term "container" is used herein to mean a receptacle for holding and/or storing a drug formulation. The container can be single-dose or multidose, and/or disposable or refillable.

The term "cassette" shall be interpreted to mean a container which holds, in a
25 protective cover, a package or a plurality of packages which packages are interconnected to each other and held in the cassette in an organized manner, e.g., interfolding or wound. The cassette is connectable to a dispensing device, which dispensing device may include a power source, e.g., one or more batteries which provide power to the dispensing device.

The term "porosity" is used herein to mean a percentage of an area of a surface area
30 that is composed of open space, e.g., a pore, hole, channel or other opening, in a membrane, nozzle, filter or other material. The percent porosity is thus defined as the total area of open space divided by the area of the material, expressed as a percentage (multiplied by 100). High

porosity (e.g., a porosity greater than 50%) is associated with high flow rates per unit area and low flow resistance. In general, the porosity of the nozzle is less than 10%, and can vary from $10^{-3}\%$ to 10%, while the porosity of the filter is at least 1%, and preferably at least 50%, porous.

5 The term "porous membrane" shall be interpreted to mean a membrane of material having any given outer parameter shape, but preferably having a convex shape, wherein the membrane has a plurality of pores therein, which openings may be placed in a regular or irregular pattern, and which pores have an unflexed diameter of their exit aperture in the range of 0.25 micron to 6 microns and a pore density in the range of 1 to 1,000 pores per
10 square millimeter for respiratory delivery. For ocular delivery, the pores have an unflexed diameter of their exit aperture in the range of 5 microns to 50 microns, preferably 7.5 to 25 microns, and a similar pore density. The porous membrane has a porosity of about 0.0005% to 0.2%, preferably about 0.01% to 0.1%. In one embodiment, the porous membrane comprises a single row of pores on, e.g., a large piece of membrane material. The pores may
15 be planar with respect to the surface of the porous membrane material, or may have a conical configuration. The membrane material is preferably hydrophobic and includes materials such as polycarbonates, polyimides, polyethers, polyether imides, polyethylene and polyesters which may have the pores formed therein by any suitable method including laser drilling or anisotropic etching through a thin film of metal or other suitable material. The membrane
20 preferably has sufficient structural integrity so that it is maintained intact (will not rupture) when subjected to force in the amount up to about 40 bar, preferably of up to about 50 bar while the formulation is forced through the pores.

 The term "low resistance filter" shall be interpreted to mean a filter of material having any given outer parameter shape, and having a plurality of openings therein, which openings
25 may be placed in a regular or irregular pattern. The openings in the filter can be of any shape, and are preferably substantially evenly distributed throughout the filter surface area. Preferably, the porosity of the low resistance filter is greater than 50%, preferably at least 60%, more preferably at least 70%. Preferably, the low resistance filter prevents passage of particles greater than about 0.5 microns in size (e.g., having a diameter greater than 0.5
30 microns). Where the filter openings are pores, the pores can have a diameter in the range of from about 0.25 micron to 6 microns for respiratory tract delivery, or from about 5 microns to 50 microns for ocular delivery. The filter has an opening density in the range of from

about 10 to 20,000,000 openings per mm². Preferably the filter has holes of about 0.5 μm positioned about 0.5 μm apart at a density of 10⁶ holes per mm². Preferably, the ratio of the pore density of the porous membrane to the low resistance filter is in the range of about 1:1.5 to about 1:100,000; the ratio of the pore diameter of the pores of the porous membrane to the diameter of the openings of the low resistance filter is in the range of from about 1:0.95 to 1:0.1. Preferably, the flow resistance of the filter is the same as or lower than the flow resistance of the porous membrane used in conjunction with the filter. The filter is preferably comprised of a material having a density in the range of 0.25 to 3.0 mg/cm², more preferably 1.7 mg/cm², and a thickness of about 10 microns to about 500 microns, more preferably about 20 to 150 microns. The filter can be made of any material suitable for use in the invention, e.g., cellulose ester, mixed cellulose ester, modified polyvinylidene fluoride, polytetrafluoroethylene, bisphen polycarbonate, borosilicate glass, silver, polypropylene, polyester, polyimide, polyether, or any suitable polymeric material. The filter material includes materials such as polycarbonates and polyesters which may have the pores formed therein by any suitable method, including anisotropic etching or by etching through a thin film of metal or other suitable material, electron discharge machining, or laser micromachining. The filter preferably has sufficient structural integrity such that it is maintained intact (i.e., will not rupture) when subjected to force up to about 35 bar, preferably up to about 50 bar during extrusion of the formulation through the pores (of filter or membrane). The porosity of the low resistance filter is 5-85%, preferably 70%, while the porosity of the nozzle is 10⁻⁴%-1%, preferably 0.001%-0.1%.

The term "flow resistance" shall be interpreted to mean the resistance associated with the passage of a liquid or aerosol through a porous material, e.g., through the porous membrane or the low resistance filter described herein. Flow resistance is affected by the size and density of pores in the porous material, the viscosity of a liquid passing through the material, and other factors well known in the art. In general, "low resistance" of the "low resistance filter" means that the flow resistance of the low resistance filter is substantially the same as or less than the flow resistance of the porous membrane used in conjunction with the low resistance filter.

The terms "drug," "active agent," "pharmaceutically active drug" and the like are used interchangeably herein to encompass compounds which are administered to a patient in order to obtain a desired pharmacological effect. The effect may be a local or topical effect in the

eye or respiratory tract such as in the case of most respiratory or ophthalmic drugs or may be systemic as with analgesics, narcotics, hormones, hematopoietic drugs, various types of peptides including insulin and hormones such as EPO. Other exemplary drugs are set forth in U.S. Patent No. 5,419,315, issued May 30, 1995, PCT Published Application WO 96/13291, published May 9, 1996, and PCT Published Application WO 96/13290, published May 9, 1996, incorporated herein by reference.

The term "respiratory drug" shall be interpreted to mean any pharmaceutically effective compound used in the treatment of any respiratory disease and in particular the treatment of diseases such as asthma, bronchitis, emphysema and cystic fibrosis. Useful "respiratory drugs" include those which are listed within the Physician's Desk Reference (most recent edition). Such drugs include beta adrenergic agonists which include bronchodilators including albuterol, isoproterenol sulfate, metaproterenol sulfate, terbutaline sulfate, pirbuterol acetate, salmeterol xinafoate, formoterol; steroids including corticosteroids used as an adjunct to beta agonist bronchodilators such as beclomethasone dipropionate, flunisolide, fluticasone, budesonide and triamcinolone acetonide; antibiotics including antifungal and antibacterial agents such as chloramphenicol, chlortetracycline, ciprofloxacin, framycetin, fusidic acid, gentamicin, neomycin, norfloxacin, ofloxacin, polymyxin, propamidine, tetracycline, tobramycin, quinolones, and the like; and also includes peptide nonadrenergic noncholinergic neurotransmitters and anticholinergics. Antiinflammatory drugs used in connection with the treatment of respiratory diseases include steroids such as beclomethasone dipropionate, triamcinolone acetonide, flunisolide and fluticasone. Other antiinflammatory drugs and antiasthmatics which include cromoglycates such as cromolyn sodium. Other respiratory drugs which would qualify as bronchodilators include anticholinergics including ipratropium bromide. Other useful respiratory drugs include leukotriene (LT) inhibitors, vasoactive intestinal peptide (VIP), tachykinin antagonists, bradykinin antagonists, endothelin antagonists, heparin furosemide, antiadhesion molecules, cytokine modulators, biologically active endonucleases, recombinant human (rh) DNase, α_1 antitrypsin and antibiotics such as gentamicin, tobramycin, cephalosporins or penicillins, nucleic acids and gene vectors. The present invention is intended to encompass the free acids, free bases, salts, amines and various hydrate forms including semihydrate forms of such respiratory drugs and is particularly directed towards pharmaceutically acceptable formulations of such drugs which are formulated in combination with pharmaceutically

acceptable excipient materials generally known to those skilled in the art—preferably without other additives such as preservatives. Preferred drug formulations do not include additional components such as preservatives which have a significant effect on the overall formulation. Thus preferred formulations consist essentially of pharmaceutically active drug and a
5 pharmaceutically acceptable carrier (e.g., water and/or ethanol). However, if a drug is liquid without an excipient the formulation may consist essentially of the drug provided that it has a sufficiently low viscosity that it can be aerosolized using a dispenser of the present invention.

The term "ophthalmic drug" or "ophthalmic treatment fluid" refers to any pharmaceutically active compound used in the treatment of any ocular disease.

- 10 Therapeutically useful compounds include, but are not limited to, (1) antiglaucoma compounds and/or compounds that decrease intraocular pressure such as β -adrenoceptor antagonists (e.g., cetamolol, betaxolol, levobunolol, metipranolol, timolol, etc.), mitotics (e.g., pilocarpine, carbachol, physostigmine, etc.), sympatomimetics (e.g., adrenaline, dipivefrine, etc.), carbonic anhydrase inhibitors (e.g., acetazolamide, dorzolamide, etc.),
15 prostaglandins (e.g., PGF-2 alpha), (2) antimicrobial compounds including antibacterial and antifungal compounds (e.g., chloramphenicol, chlortetracycline, ciprofloxacin, framycetin, fusidic acid, gentamicin, neomycin, norfloxacin, ofloxacin, polymyxin, propamidine, tetracycline, tobramycin, quinolones, etc.), (3) antiviral compounds (e.g., acyclovir, cidofovir, idoxuridine, interferons, etc.), (4) aldose reductase inhibitors (e.g., tolrestat, etc.), (5)
20 antiinflammatory and/or antiallergy compounds (e.g., steroidal compounds such as betamethasone, clobetasone, dexamethasone, fluorometholone, hydrocortisone, prednisolone, etc. and nonsteroidal compounds such as antazoline, bromfenac, diclofenac, indomethacin, lodxamide, saprofen, sodium cromoglycate, etc.), (6) artificial tear/dry eye therapies, comfort drops, irrigation fluids, etc. (e.g., physiological saline, water, or oils; all optionally containing
25 polymeric compounds such as acetylcysteine, hydroxyethylcellulose, hydroxymellose, hyaluronic acid, polyvinyl alcohol, polyacrylic acid derivatives, etc.), (7) local anaesthetic compounds (e.g., amethocaine, lignocaine, oxbuprocaine, proxymetacaine, etc.), (8) compounds which assist in the healing of corneal surface defects (e.g., cyclosporine, diclofenac, urogastrone and growth factors such as epidermal growth factor), (9) mydriatics
30 and cycloplegics (e.g., atropine, cyclopentolate, homatropine, hyoscine, tropicamide, etc.), (10) compounds for the treatment of pterygium (e.g., mitomycin C., collagenase inhibitors such as batimastat, etc.), (11) compounds for the treatment of macular degeneration and/or

diabetic retinopathy and/or cataract prevention, (12) compounds for systemic effects following absorption into the bloodstream after ocular administration (e.g., insulin, narcotics, analgesics, anesthetics).

The terms "diagnostic" and "diagnostic agent" and the like are used interchangeably herein to describe any compound that is delivered to a patient in order to carry out a diagnostic test or assay on the patient. Such agents are generally tagged with a radioactive or fluorescent component or other component which can be readily detected when administered to the patient. Exemplary diagnostic agents include, but are not limited to, methacholine, histamine, salt, specific allergens (such as pollen or pollen extracts), sulphites, and imaging agents for magnetic resonance imaging and/or scintigraphy. Diagnostic agents can be used to, for example, assess bronchial constriction in patients having or suspected of having cystic fibrosis or asthma. Radiolabelled aerosols can be used to diagnose pulmonary embolism, or to assess mucociliary clearance in various chronic obstructive diseases of the lung. Diagnostic agents can also be used to assess ophthalmic conditions. Exemplary ocular diagnostic agents include, but are not limited to, such compounds as fluorescein or rose bengal.

The term "formulation" is intended to encompass any drug or diagnostic agent formulation which is delivered to a patient using the present invention. Such formulations generally include the drug or diagnostic agent present within a pharmaceutically acceptable inert carrier. The formulation is generally in a liquid flowable form which can be readily aerosolized, the particles having a particle size in the range of 0.5 to 12 microns in diameter for respiratory administration. Formulations can be administered to the patient using device of the invention can be administered by nasal, intrapulmonary, or ocular delivery.

The terms "aerosol," "aerosolized formulation," and the like, are used interchangeably herein to describe a volume of air which has suspended within it particles of a formulation comprising a drug or diagnostic agent wherein the particles have a diameter in the range of 0.5 to 12 microns, for respiratory therapy, or in the range of 15 to 50 microns for ocular therapy.

The term "aerosol-free air" is used to describe a volume of air which is substantially free of other material and, in particular, substantially free of particles of respiratory drug.

The term "dosing event" shall be interpreted to mean the administration of drug or diagnostic agent to a patient by the ocular or respiratory (e.g., nasal or intrapulmonary) route

of administration (i.e., application of a formulation to the patient's eye or to the patient's respiratory tract by inhalation of aerosolized particles) which event may encompass one or more releases of drug or diagnostic agent formulation from a dispensing device over a period of time of 15 minutes or less, preferably 10 minutes or less, and more preferably 5 minutes or less, during which period multiple administrations (e.g., applications to the eye or inhalations) may be made by the patient and multiple doses of drug or diagnostic agent may be released and administered. A dosing event shall involve the administration of drug or diagnostic formulation to the patient in an amount of about 10 μ l to about 1,000 μ l in a single dosing event. Depending on the drug concentration in the formulation, a single package may not contain sufficient drug for therapy or diagnosis. Accordingly, a dosing event may include the release of drug or diagnostic agent contained from several containers of a package held in a cassette or the drug or diagnostic agent contained within a plurality of such containers when the containers are administered over a period of time, e.g., within 5 to 10 minutes of each other, preferably within 1-2 minutes of each other.

The term "velocity of the drug" or "velocity of particles" shall mean the average speed of particles of drug or diagnostic agent formulation moving from a release point such as the porous membrane of the nozzle or a valve to a patient's mouth or eye. In a preferred embodiment pertaining to respiratory therapy, the relative velocity of the particles is zero or substantially zero with reference to the flow created by patient inhalation.

The term "bulk flow rate" shall mean the average velocity at which air moves through a channel.

The term "flow boundary layer" shall mean a set of points defining a layer above the inner surface of a channel through which air flows wherein the air flow rate below the boundary layer is substantially below the bulk flow rate, e.g., 50% or less than the bulk flow rate.

The term "carrier" shall mean a flowable, pharmaceutically acceptable excipient material, preferably a liquid, flowable material, in which a drug or diagnostic agent is suspended in or more preferably dissolved in. Useful carriers do not adversely interact with the drug or diagnostic agent and have properties which allow for the formation of aerosolized particles, which particles preferably have a diameter in the range of 0.5 to 12.0 microns that are generated by forcing a formulation comprising the carrier and drug or diagnostic agent through pores having an unflexed diameter of 0.25 to 6.0 microns for delivery to the

respiratory tract. Similarly, a useful carrier for delivery to the eye does not adversely interact with the drug or diagnostic agent and has properties which allow for the formation of aerosolized particles, which particles preferably have a diameter of 15 to 50 microns and are generated by forcing the formulation comprising the carrier and drug or diagnostic agent through pores 7.5 to 25 microns in relaxed diameter. Preferred carriers include water, ethanol, saline solutions and mixtures thereof, with pure water being preferred. Other carriers can be used provided that they can be formulated to create a suitable aerosol and do not adversely affect human tissue or the drug or diagnostic agent to be delivered.

The term "measuring" describes an event whereby the (1) total lung capacity, (2) inspiratory flow rate or (3) inspiratory volume of the patient is measured and/or calculated and the information used in order to determine an optimal point in the inspiratory cycle at which to release an aerosolized and/or aerosol-free volume of air. An actual measurement of both rate and volume may be made or the rate can be directly measured and the volume calculated based on the measured rate. The total lung capacity can be measured or calculated based on the patient's height, sex and age. It is also preferable to continue measuring inspiratory flow during and after any drug delivery and to record inspiratory flow rate and volume before, during and after the release of drug. Such reading makes it possible to determine if drug or diagnostic agent was properly delivered to the patient.

The term "monitoring" shall mean measuring lung functions such as inspiratory flow, inspiratory flow rate, and/or inspiratory volume so that a patient's lung function as defined herein, can be evaluated before and/or after drug delivery thereby making it possible to evaluate the effect of drug delivery on, for example, the patient's lung function.

The term "inspiratory flow profile" shall be interpreted to mean data calculated in one or more events measuring inspiratory flow and cumulative volume, which profile can be used to determine a point within a patient's inspiratory cycle which is optimal for the release of drug to be delivered to a patient. An optimal point within the inspiratory cycle for the release of an aerosol volume is based, in part, on (1) a point most likely to deliver the aerosol volume to a particular area of a patient's respiratory tract, in part on (2) a point within the inspiratory cycle likely to result in the maximum delivery of drug and, in part, on (3) a point in the cycle most likely to result in the delivery of a reproducible amount of drug to the patient at each release of drug. The criteria 1-3 are listed in a preferred order of importance. However, the order of importance can change based on circumstances. The area of the respiratory tract

being treated is determined by adjusting the volume of aerosol-containing or aerosol-free air and/or by adjusting the particle size of the aerosol. The repeatability is determined by releasing at the same point in the respiratory cycle each time drug is released. To provide for greater efficiency in delivery, the drug delivery point is selected within given parameters.

5 The terms "formulation" and "flowable formulation" and the like are used interchangeably herein to describe any pharmaceutically active drug (e.g., a respiratory drug, or drug that acts locally or systemically, and that is suitable for respiratory delivery) or diagnostic agent combined with a pharmaceutically acceptable carrier in flowable form having properties such that it can be aerosolized to particles having a diameter of 0.5 to 12.0 microns
10 for respiratory therapy, or 15 to 75 microns for ocular therapy. Such formulations are preferably solutions, e.g., aqueous solutions, ethanolic solutions, aqueous/ethanolic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. Preferred formulations are drug(s) and/or diagnostic agent(s) dissolved in a liquid, preferably in water.

 The term "substantially dry" shall mean that particles of formulation include an
15 amount of carrier (e.g., water or ethanol) which is equal to (in weight) or less than the amount of drug or diagnostic agent in the particle, more preferably it means free water is not present.

 The terms "aerosolized particles" and "aerosolized particles of formulation" shall mean particles of formulation comprised of carrier and drug and/or diagnostic agent that are formed
20 upon forcing the formulation through a nozzle, which nozzle comprises a flexible porous membrane. Where respiratory therapy is desired, the particles are of a sufficiently small size such that when the particles are formed, they remain suspended in the air for a sufficient amount of time for inhalation by the patient through his nose or mouth. Where ocular therapy is desired, the particles formed are of a size optimal for application to the eye. Preferably,
25 particles for respiratory delivery have a diameter of from about 0.5 micron to about 12 microns, and are generated by forcing the formulation through the pores of a flexible porous membrane, where the pores have an unflexed exit aperture diameter in the range of about 0.25 micron to about 6.0 microns. More preferably, the particles for respiratory delivery have a diameter of about 1.0 to 8.0 microns with the particles created by being
30 moved through pores having an unflexed exit aperture diameter of about 0.5 to about 4 microns. For ocular delivery, the particles have a diameter from about 15 micron to about 75 microns, and are generated by forcing the formulation through the pores of a flexible

porous membrane, where the pores have an unflexed exit aperture diameter in the range of about 5 micron to about 50 microns. More preferably, the particles for ocular delivery have a diameter of about 15 to 50 microns, and can be generated by forcing the formulation through flexible membrane pores having an unflexed exit aperture diameter of about 7.5 to about 25
5 microns. In either respiratory or ocular delivery, the flexible membrane pores are present at about 10 to 10,000 pores over an area in size of from about 1 sq. millimeter to about 1 sq. centimeter, preferably from about 1×10^1 to about 1×10^4 pores per square millimeter, more preferably from about 1×10^2 to about 3×10^4 pores per square millimeter, and the low resistance filter has an opening density in the range of 20 to 1,000,000 pores over an area of
10 about one square millimeter.

The term "substantially through" with reference to the pores being formed in the membrane or material shall mean pores which either completely traverse the width of the membrane or are formed to have a thin peelable layer over their exit aperture. The pores formed with a peelable layer over their exit apertures are formed so as to peel outward at a
15 substantially lower pressure than would be required to rupture the membrane in the nonporous areas.

GENERAL OVERVIEW OF THE METHODOLOGY OF THE INVENTION

We have now invented a method of forming nozzles of small, uniform size that permit
20 the generation of uniform aerosols of diagnostic and therapeutic agents which can then be administered to particular target tissues such as the eye or specific areas of the respiratory tract. The method comprises directing a laser source onto a thin material so as to form pores substantially through the material. The pores may be formed either individually or simultaneously. The laser source may be controlled using a mask and/or beam-splitting or
25 focusing techniques.

The material used may be any material from which suitable pores can be formed and which does not adversely interact with other components of the delivery device, particularly with the formulation being administered. In a preferred embodiment, the material is a flexible polymeric organic material, for example a polyether, polycarbonate, polyimide, polyether
30 imide, polyethylene or polyester. Flexibility of the material is preferred so that the nozzle can adopt a convex shape and protrude into the airstream upon application of pressure, thus forming the aerosol away from the static boundary layer of air. The membrane is preferably

about 10 to about 100 μm in thickness, more preferably from about 12 to about 45 μm in thickness. A preferred material is a 25 μm thick film of polyimide. Considerations for the membrane material include the ease of manufacture in combination with the formulation container, flexibility of the membrane, and the pressure required to generate an aerosol from pores spanning a membrane of that thickness and flexibility.

The particular laser source used in the method of the invention will to some extent be determined by the material in which the pores are to be formed. Generally, the laser source must supply a sufficient amount of energy of a wavelength which can form an effective aerosolization nozzle in the material being ablated. Typically the wavelength can be from about 250 to about 360 nm.

The output of the particular laser source can be manipulated in a variety of ways prior to being applied to the material. For example, the frequency can be doubled or tripled using, for example, a lithium triborate crystal or series of crystals using a type I process, a type II process or a combination thereof. This laser beam can be further split into multiple beams to create multiple pores simultaneously. The beam can also be directed through a mask or spatially filtered, and can also be expanded prior to focusing.

One laser effective for such nozzles is a neodymium-yttrium aluminum garnet laser. This laser is a pulsed ultraviolet wavelength light source which provides sufficiently high peak power in short pulses to permit precise ablation in a thin material. The beam profile from this laser is radially symmetric which tends to produce radially symmetric pores.

Another laser effective for creating pores in materials such as polyethers and polyimide is an excimer laser. This laser produces ultraviolet wavelength light, similar to the Nd:YAG laser. However, the beam is not radially symmetrical but can be projected through a mask to simultaneously drill one or more conical or cylindrical holes. Preferably, the laser source is an excimer laser providing a wavelength of 308 nm. The energy density used for such a laser typically ranges from about 525 to about 725 mJ/cm^2 , and is preferably about 630 mJ/cm^2 . Using such a laser on a 25 μm thick polyimide membrane, the number of pulses is typically about 100 to about 200.

For respiratory delivery, the pores are formed so as to have an unflexed exit aperture diameter from about 0.5 to about 6 μm , preferably about 1-2 μm . For ocular delivery, the pores are formed so as to have an unflexed exit aperture diameter in the range of 5 microns to 50 microns, preferably 7.5 to 25 microns. The pores can be spaced from about 10 to about

1000 μm apart or more, but are preferably spaced from about 30 to about 70 μm apart, most preferably about 50 μm apart. The pore spacing is determined in part by the need to prevent the aerosol from adjacent pores from adversely interfering with each other, and in part to minimize the amount of membrane used and the associated manufacturing difficulties and costs. The pore spacing is preferably fairly uniform, with a variability in the interpore distance of preferably less than about 20%, more preferably less than about 10%, and most preferably about 2% or less (<1 μm variability for pores spaced 50 μm apart).

The pores may be roughly cylindrical or conical in shape, where "cylindrical" means that the pores pass perpendicularly through the membrane and have approximately the same diameter on each surface of and throughout the membrane, and "conical" means that the pores are larger on one side of the membrane than on the other side, and includes instances where the cross-section of the pores is conical, curved or where the diameter of the pore is reduced stepwise. Preferably, the pores are conical. When the pores are conical, the wider diameter of the cone is found on the entrance side of the pore to which the formulation is applied under pressure, while the smaller diameter of the cone is found on the exit side of the pore from which aerosolization occurs. For example, for respiratory delivery, when the exit aperture of the holes is about 0.6 to about 1.5 μm in diameter, the entrance aperture preferably has a diameter of from about 4 to about 12 μm , more preferably from about 6 to about 12 μm . The aperture size is preferably uniform; following the methods taught herein, the variability in diameter of each hole having a 1.25 μm aperture is no more than 0.05 μm , and for a 6 μm aperture is no more than 0.1 μm . The nozzle may be provided as an integral part of the formulation packaging, or may be provided separately, for example integrally with the inhalation device, or wound on a roll for disposable use.

In an alternative embodiment, the pores are incompletely formed so that a thin peelable layer remains covering the exit apertures of the pores. This peelable layer bursts outward upon forcible application of the drug formulation to the nozzle during drug delivery, permitting aerosolization of the formulation. The peelable layer of the pores is formed so as to have a breaking pressure significantly below that of the overall membrane, and the pressure at which the layer bursts is significantly below that applied in the normal course of drug administration, so that the pores burst substantially uniformly and completely. The incompletely formed pores may be formed by application of a thin layer of material to the

outer side of the membrane after formation of complete pores, or by incompletely ablating holes through the membrane.

Any number of pores may be formed in the material comprising the nozzle apparatus. The number of nozzles is determined in part by the amount of formulation which must be delivered for a given application, and therefore the potency and concentration of the agent being administered must be taken into account. Additionally, the period of time over which the formulation is to be administered must also be considered. In one embodiment of the invention, the pores are formed in a 7x48 array of pores spaced 50 μm apart. For a given pore exit diameter and formulation pressure, hole number can be adjusted to control delivery time. For example, if the expression $N=356 \cdot d^{-667}$ is used, the pressure required for a 1.2 second delivery time at each hole size will give robust aerosol generation.

In another embodiment, the pores are provided with elevated areas surrounding the exit aperture, so as to prevent liquid from intruding from the outer surface of the membrane back into the pore and thereby disrupting aerosolization. The elevated areas may be of any shape, such as circular or rectangular, or may be irregularly shaped. The elevated areas can be constructed by any suitable means, for example by etching away portions of the outer layer of the membrane, by laser drilling procedures which lead to sputtering of material around the pores, by molding or casting, by deposition of material via a mask in locations where pores are to be formed, and the like. Figure 2 shows an example of a pore formed so as to have an elevated area via excimer laser ablation from the opposite side of the membrane. The formation of the elevated area via excimer laser ablation can be controlled by altering the pulse number: a minimal number of pulses used to penetrate the membrane will form an elevated area around the aperture on the opposite side of the membrane; increasing the number of pulses will then remove this elevated area. For example, for a 25 micron thick polyimide membrane, 120 pulses of a 308 nm excimer laser at an energy density of 630 mJ/cm^2 will form a pore having an elevated area, while increasing the number of pulses above 150 will remove the elevated area and slightly widen the pore aperture. The elevated areas may be of any suitable dimensions, but preferably extend significantly less than the interpore distance so as to provide lower areas where fluid is sequestered. The elevated areas can be made from any suitable material, for example the material comprising the bulk of the membrane, or may be made from materials with desirable properties such as hydrophobicity

or solvent or drug repellence so as to repel the drug formulation from entering the exit aperture of the pores.

The invention provides a method for fabricating a porous membrane useful for delivering any type of drug or diagnostic agent to a patient by ocular administration or inhalation in the form of an aerosol having a desired aerosol particle size and having substantially no undesirable particles within the aerosol that would substantially affect the accuracy of the dose of drug or diagnostic agent delivered in the aerosol. Moreover, certain embodiments of the devices and methodology used do not require the release of low boiling point propellants in order to aerosolize drug, which propellants are conventionally used in connection with hand-held metered dose inhalers. However, like conventional hand-held metered dose inhalers, the devices used in conjunction with the present invention can be hand-held, self-contained, highly portable devices which provide a convenient means of delivering drugs or diagnostic agents to a patient via the respiratory route.

In general, an aerosol for respiratory or ocular delivery is generated from a drug or diagnostic agent formulation, preferably a flowable formulation, more preferably a liquid, flowable formulation. The drug or diagnostic agent formulation can be contained within a multidose container or within a container portion of a disposable package, where the container of the disposable package has at least one surface that is collapsible. The aerosol is generated by applying pressure of 50 bar or less, preferably 40 bar or less, to the collapsible container surface, thereby forcing the contents of the container through a nozzle array comprised of a porous membrane. Alternatively, the formulation is first forced through a low resistance filter and then through the porous membrane. The porous membrane may be rigid or flexible. Preferably the porous membrane is flexible so that upon application of the pressure required to aerosolize the formulation (i.e., preferably 50 bar or less, more preferably 40 bar or less), the nozzle's porous membrane becomes convex in shape, thus delivering the aerosolized drug or diagnostic agent into the flow path of the delivery device in a region beyond the flow boundary layer. The low resistance filter has a porosity the same as or preferably greater than the porosity of the porous membrane to provide for an overall flow resistance that is preferably lower than the flow resistance of the nozzle. The low resistance filter thus prevents particles of an undesirable size from reaching the nozzle, thereby lessening clogging of the nozzle from the inside, and filters out such undesirable particles before the

aerosol for delivery is generated, thereby avoiding delivery of undesirable particles to the patient.

The formulations for aerosolization can include preservatives or bacteriostatic type compounds. However, the formulation preferably comprises a pharmaceutically active drug (or a diagnostic agent) and a pharmaceutically acceptable carrier such as water. The formulation can be primarily or essentially composed of the drug or diagnostic agent (i.e., without carrier) if the drug or diagnostic agent is freely flowable and can be aerosolized. Useful formulations include, for example, formulations currently approved for use with nebulizers or for injections.

In general, the low-resistance filter and nozzle comprised of a porous membrane formed according to the invention can be used in conjunction with any container suitable for containing a drug or diagnostic agent formulation of interest. The container can be, for example, a single-dose container or a multidose container. The containers can be refillable, reusable, and/or disposable. Preferably, the container is disposable. The container can be designed for storage and delivery of a drug or diagnostic agent that is dry, substantially dry, liquid, or in the form of a suspension. The container may be any desired size. In most cases the size of the container is not directly related to the amount of drug or diagnostic agent being delivered in that most formulations include relatively large amounts of excipient material, e.g., water or a saline solution. Accordingly, a given size container could include a wide range of different doses by varying drug (or diagnostic agent) concentration.

The container can also be one that provides for storage of a drug or diagnostic agent in a dry or substantially dry form until the time of administration, at which point, if desired, the drug or diagnostic agent can be mixed with water or other liquid. An exemplary dual compartment container for carrying out such mixing of dry drug with liquid just prior to administration is described in copending U.S. application serial no. 08/549,295, filed October 27, 1995, incorporated herein by reference with respect to such containers.

In a preferred embodiment, the containers useful with the invention comprise a single-use, single-dose, disposable container that holds a formulation for delivery to a patient and has a collapsible wall. In addition, the container can be configured in the same package with a porous membrane and a low resistance filter, where the low resistance filter is positioned between the porous membrane and a formulation contained in the container. The container is preferably disposable after a single use in the delivery of the formulation contained therein.

The low resistance filter and the nozzle can be included as components of a disposable package that is composed of a container that serves as a storage receptacle for the drug formulation, a porous membrane, and a low resistance filter positioned between the drug formulation and the nozzle.

5 The low resistance filter and the nozzle can also be provided separate from the drug container and/or the disposable package. For example, the low resistance filter can be provided as a single disposable filter that can be inserted in the proper position between the formulation in the container and a nozzle, which can also be provided as a single disposable unit. The disposable filter and disposable nozzle can be inserted prior to use and can be
10 disposed after each use or after a recommended number of uses.

Alternatively, the low resistance filter and nozzle can be provided as a separate ribbon or ribbons.

AEROSOL DELIVERY DEVICES:

15 In general, aerosol delivery devices useful with nozzles formed by the method of the invention comprise (a) a device for holding a formulation-containing container, preferably a disposable container, with at least one but preferably a number of containers, and (b) a mechanical mechanism for forcing the contents of a container (on the package) through a low resistance filter and a nozzle comprised of a porous membrane. Where the device is used for
20 respiratory delivery, the device can further comprise (c) a means for controlling the inspiratory flow profile, (d) a means for controlling the volume in which the drug or diagnostic agent is inhaled, (e) a switch for automatically releasing or firing the mechanical means to release a determined volume of aerosol and aerosol-free air when the inspiratory flow rate and/or volume reaches a predetermined point, (f) a means for holding and moving
25 one package after another into a drug release position so that a new package is positioned in place for each release of drug, and (g) a source of power, e.g., spring, or conventional batteries or other source of electric power.

 The aerosol delivery devices of the invention can also comprise additional components such as, but not limited to, a monitor for analyzing a patient's inspiratory flow, a heating
30 mechanism for adding energy to the air flow into which the aerosol particles are released, means for measuring ambient temperature and humidity, screens to prevent undesirable particles in the environment from entering the flow path, and/or other components that might

enhance aerosol delivery and/or patient compliance with an aerosol delivery regimen. The device can also comprise components that provide or store information about a patient's aerosol delivery regimen and compliance with such, the types and amounts of drug delivered to a patient, and/or other information useful to the patient or attending physician. Suitable
5 devices are described in U.S. Patent No. 5,544,646, issued August 13, 1996; U.S. Patent No. 5,497,763, issued March 12, 1996; PCT published application WO 96/13292, published May 9, 1996; and PCT published application WO 9609846, published April 4, 1996, each of which is incorporated herein by reference with respect to such aerosol delivery devices.

These devices can obtain power from a plug-in source; however, the device is
10 preferably a self-contained, portable device that is battery powered. For example, the methodology of the invention can be carried out using a portable, hand-held, battery-powered device which uses a microprocessor (e.g., as the means for recording a characterization of the inspiratory profile) as per U.S. Patents No. 5,404,871, issued April 11, 1995, and No. 5,450,336, issued September 12, 1995, incorporated herein by reference. The
15 microprocessor is programmed using the criteria described herein using the device, dosage units, and system disclosed in PCT Application US94/05825 with modifications as described herein. Alternatively, the methodology of the invention can be carried out using a mechanical (nonelectronic) device. Those skilled in the art would recognize that various components can be mechanically set to actuate at a given inspiratory flow rate and at a given volume (e.g., a
20 spinnable flywheel which rotates a given amount per a given volume).

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention.
25 Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

All patents, patent applications, and publications mentioned herein are hereby incorporated by reference in their entirety.

EXAMPLES

EXAMPLE 1: PREPARATION OF NOZZLES

Nozzles were prepared from thin-film polyimide (25 μm , Kapton™ Type 100H, DuPont) using a laser (Uniphase, model s355B-100Q). The film was held by a vacuum platen to a three axis stage.

To determine the effect of power level and number of pulses on pore size, the power and pulse number was varied in a systematic fashion as pores were drilled in a single piece of Kapton. A second order polynomial fit of the pore size vs. power level was performed, and was used to estimate the power required to drill pores of diameter 1, 1.5, and 2 μm . Sample nozzles were fabricated at various power levels, and pores on each sample were sized, and the average size computed. This process was iterated until a power level was determined that gave an average pore size within 5% of the desired value.

Table I: Power Level vs Pore Size

Desired Pore Size	Power Level Used
1.0 μm	1.1 mW
1.5 μm	1.5 mW
2.0 μm	1.9 mW

Nozzles for the experiments below were fabricated at these settings. The power was checked and adjusted after every 10 nozzles.

To determine pore size, nozzles were imaged using a scanning electron microscope (Philips, model 505). The samples were coated by gold deposition (Denton Desk II, 45 μA , 120 seconds) prior to imaging. The images were digitized at video resolution using a frame grabber (Data Translation DT3152). Video frames (64) were averaged to create a final image, which was stored to disk. After 10 images had been acquired in this manner, they were read into an image processing software package (Optimus, version 6.0). A macro was developed that determined the perimeter of the pores by thresholding, and based on this perimeter, an area equivalent diameter was calculated. The area equivalent diameter determined for the 10 pores was averaged to determine the final diameter.

EXAMPLE 2:**Purpose:**

To determine the effect of variable exit hole size on the emitted dose and aerosol quality obtained with Excimer Nozzles.

- 5 The nozzle lots used in this experiment were designed to have exit hole sizes of approximately 0.8 - 1.5 μM .

ED, MMAD, GSD and FPD results were measured.

ED - fraction of the loaded dose that is emitted from the device

- 10 MMAD - mass median aerodynamic diameter

GSD - geometric standard deviation

FPD - fine particle dose (fraction of the dose loaded in the jacket that exits the mouthpiece in particles < 3.5 μM aerodynamic diameter

- 15 Packet Preparation: the nozzles were drilled using a UV excimer laser. After scanning electron microscopy (SEM) to examine a portion of the nozzles, the remaining nozzle file was sealed to blister jackets. The test liquid was 45 μl of cromolyn sodium (30 mg/ml) aqueous solution.

SUMMARY PERFORMANCE DATA

20	SEM exit hole size (μm) from different sub-lots	ED (%)	MMAD (μm)	GSD
	1.32 \pm 0.05 1.45 \pm 0.08	72.3 \pm 3.9	2.51	1.48
25	1.20 \pm 0.1 1.38 \pm 0.05	68.2 \pm 1.5	2.68	1.44
	1.40 \pm 0.05	73.4 \pm 6.1	2.60	1.41
	0.51 \pm 0.13	67.13 \pm 6.95	1.67	1.39
	0.81 \pm 0.09	72.04 \pm 2.72	2.38	1.41
30	0.82 \pm 0.16	75.96 \pm 6.9	2.20	1.44

Figure 3 shows that MMAD increases with hole size as expected.

EXAMPLE 3:

A porous membrane suitable for aerosol delivery of a diagnostic or therapeutic agent is fabricated. A 7x48 array of pores spaced 50 μm apart is ablated in a 25 μm thick polyimide film using a 308 nm excimer laser at 600 mJ/cm² with a 5X projection system and 105 pulses.

- 5 The laser source is directed through a suitable mask to generate the array in the polyimide. The beam is directed using a lens so that the entrance diameter of the pores thus formed is 6 microns and the exit diameter of the pores is 1.1 microns.

What is claimed is:

1. A method for making a nozzle for aerosolization of a therapeutic or diagnostic agent, comprising:

providing a laser source;

5 providing a thin substantially planar material suitable for use in aerosolizing said agent; and

directing said laser source onto said material in a manner and for a time suitable to ablate a plurality of substantially circumferential pores substantially through said planar material, wherein each of said pores has the same first aperture diameter with a standard deviation in
10 pore diameter of less than about 10 %.

2. The method of claim 1, wherein the material is a polymeric organic material having a thickness of from about 10 to about 100 μm ;

wherein the first aperture of each of said pores has an unflexed diameter of from about
15 0.5 to about 25 μm ; and

wherein from about 0.1 to about 10 mW average power per pore are provided by said laser source to ablate the material.

3. The method of claim 1, wherein the laser source is a UV excimer laser having
20 a wavelength of 308 nm.

4. The method of claim 3, wherein the excimer energy density is from about 525 to about 725 mJ/cm^2 .

25 5. The method of claim 1, wherein the laser source is a neodymium-yttrium aluminum garnet laser providing a beam having a wavelength of 355 nm.

6. The method of claim 2, wherein the material is selected from polycarbonates, polyimides, polyethers, polyether imides, polyethylene and polyesters; and
30 wherein the polymeric material has a thickness in the range of about 15 to 40 microns.

7. The method of claim 1, wherein the pores are individually ablated and wherein a second exit aperture of each of said pores has a diameter greater than the first aperture.

8. The method of claim 1, wherein the pores are simultaneously ablated and the pores are regularly spaced in rows.

9. The method of claim 1, wherein said laser source is directed through a mask prior to striking said material.

10. The method of claim 1, wherein said pores are completely ablated through said material.

11. The method of claim 10, wherein a second exit aperture of each pore is surrounded by an elevated area projecting above the substantially planar membrane.

12. The method of claim 11, wherein the elevated areas are formed by depositing elevated areas on the membrane and making pores in the membrane through the elevated areas.

13. The method of claim 11, wherein the elevated areas are formed by etching away surrounding areas to leave elevated areas on the membrane and making pores through the elevated areas.

14. The method of claim 6, wherein the thickness is in the range of about 20 to 30 microns; and wherein said pores are spaced from about 30 to about 70 μm apart from each other.

15. The method of claim 6, wherein the thickness is about 25 microns; and wherein said pores are spaced about 50 μm apart from each other.

16. The method of claim 1, wherein the pores are formed so that a layer of material covers an exit aperture of each pore, wherein the pores burst outward upon application of a pressure that does not otherwise rupture the membrane.

5 17. The method of claim 16, wherein the pores extend from about 70 to about 95 % of the way through the membrane.

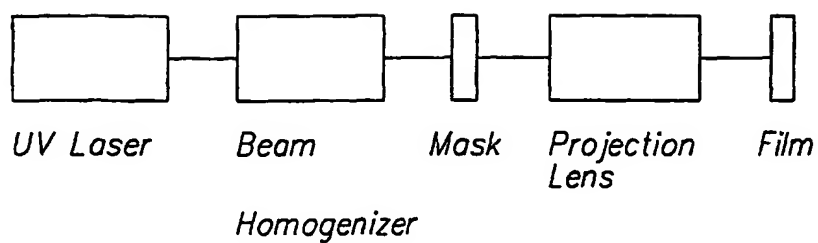
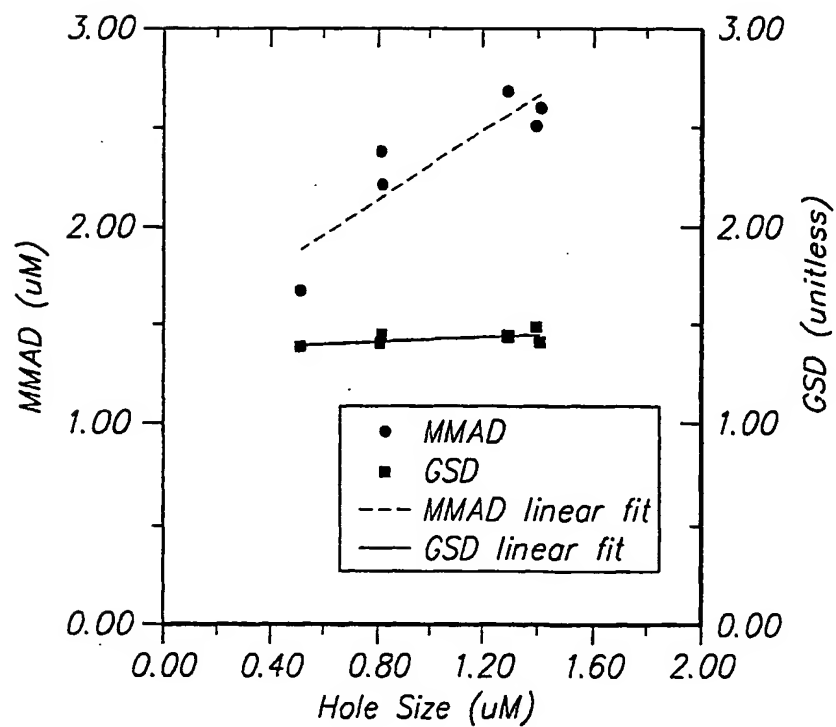
18. The method of claim 1, wherein the material has 100 or more pores.

10 19. The method of claim 1, wherein the material has 200 or more pores and wherein the laser source is controlled by interposing an opaque mask in the form of a spatial filter in an image plane of the planar material between the laser source and the planar material.

20. The method of claim 15, wherein the variability in pore spacing is less than
15 about 10%.

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1/2

**FIG. 1****FIG. 3**

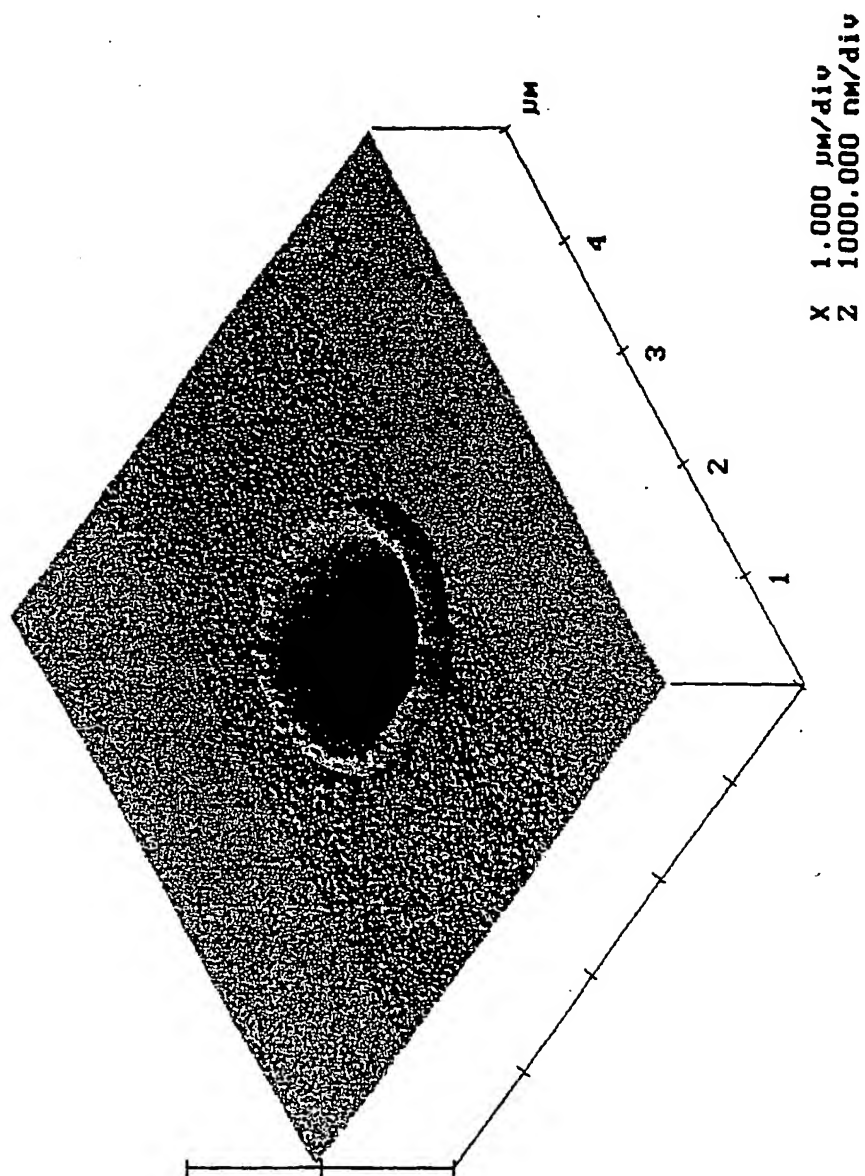


FIG. 2

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US99/26425

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : B23K 26/06

US CL : 264/400

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 219/121.61, 121.75, 121.8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST Text Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,923,608 A (FLOTTMANN et al.) 08 MAY 1990, see entire reference	1,3,7-10,11
Y	US 4,478,596 A (MICHELSON) 23 OCTOBER 1984, col. 4, line 52 through col. 5, line 23.	5
Y	US 5,486,546 A (MATHIESEN et al.) 23 JANUARY 1996, see entire reference	2,4
Y	WO 93/11861 (POURNOOR et al.) 24 JUNE 1993, see entire reference	6,14-20
Y	US 4,568,632 A (BLUM et al.) 04 FEBRUARY 1986, see entire reference	2,4
Y	US 4,234,637 A (SEWELL et al.) 18 NOVEMBER 1980, see entire reference	1,6,15

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,753,014 A (VAN RIJN) 19 MAY 1998, see entire reference	12,13
Y	US 4,234,637 A (SEWELL et al.) 18 NOVEMBER 1980, see entire reference	1,6,15

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